#13/dec.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE		
	Application Number	09/716,320
	Filing Date	November 21, 2000
	First Named Inventor	Esther H. Chang
	Group Art Unit	1635
	Examiner Name	Mary M. Schmidt
	Attorney Docket Number	2444-109
Title of the Invention: Compositions and Methods for Reducing Radiation and Drug Resistance in Cells		

Declaration Pursuant to 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Esther Chang, declare that:

1. I am the same Esther Chang named as an inventor on the above-referenced patent application.

corrected 9/16/03

2. I received a B.A. degree in biology from Fu Jen University in Taiwan in 1968 and a Ph.D. in microbiology from Southern Illinois University in 1974. From 1982-1994 I held the positions of Assistant Professor, Associate Professor, and then Professor in the Department of Pathology, Uniformed Services University of the Health Sciences in Bethesda, MD. I also was a Research Professor in their Department of Surgery and the Director of their Tumor Biology Program. From 1994-1996 I held the position of Professor of Surgery (Research), Division of Otolaryngology/Head and Neck Surgery in the Department of Surgery at Stanford University Medical Center. Since 1996, I have held the position of Professor of Surgery (Consultant) there. I currently also hold the positions of Professor of Otolaryngology, Department of Otolaryngology/Head & Neck Surgery and Professor

of Oncology, Departments of Oncology and Otolaryngology, at the Georgetown University Medical Center, Lombardi Cancer Center, and have held those positions since 1996 and 1999, respectively. A copy of my curriculum vitae is attached hereto.

3. I have read the Office Action issued by the U.S. Patent and Trademark Office on January 2, 2003, and understand the grounds of rejection set forth therein.

4. In the Office Action, claims 3-5, 7, 8, 12-14, 16 and 17 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification teaches only one specific example of a HER-2 antisense sequence and so does not provide a representative number of species of HER-2 for the claimed functions of reducing radiation or drug resistance in any cell or person. The examiner asserted that one of ordinary skill in the art could not easily determine a representative number of species of HER-2 antisense having the claimed functions.

5. The selection of effective antisense oligonucleotides is not haphazard and unpredictable. As is taught in the application, it is recognized in the art that oligos substantially complementary to an RNA sequence at or near the initiation codon of the gene of interest typically are specific to the gene. In addition, oligos complementary to an RNA sequence around the promoter sequence or at single-stranded loops typically are specific to the gene. In addition, we teach that desirably sequences are constructed that are at least 8 nucleotides long but no more than about 40 nucleotides long. Preferably the sequences are between about 15 and 20 nucleotides.

6. In the course of our studies on the use of antisense oligonucleotides directed against HER-2 as an antisense therapeutic, we have identified and tested a number of anti-HER-2 antisense molecules for their ability to down modulate HER-2 expression. In addition to the oligonucleotide identified in the application as Seq ID NO:3, one additional sequence around the

initiation codon (A); one in the promoter region (B); one in the 5` untranslated region (C); and two within the coding region (D, E) of the HER-2 gene were identified and tested by Western blot analysis. Although the oligo identified as Seq ID NO:3 displayed the highest level of anti-HER-2 effect, all of these sequences had antisense activity in human tumor cell lines.

A-Sequence 170-200, initiation codon

5`-AGC GGC ACA AGG CCG CCA GCT CCA TGG TGC-3`

B-Sequence 458-488, promoter region

5`CAC AAC TTC ATT CTT ATA CTT CCT CAAGCA-3`

C-Sequence 664-678, 5`-untranslated region

5`-TGG ACC CGG CTG GGA-3`

D-Sequence 967-981, coding region

5′-GGT TGT GAG CGA TGA-3`

E-Sequence 853-867, coding sequence

5`-CCT GGT AGA GGT GGC-3`

*Note: Underlined areas refer to areas complementary to single stranded regions of HER-2 RNA.

7. In addition, it is well known in the antisense art that once an oligo which a desired activity has been identified, it can be modified in any of several ways to increase its stability and ability to target a specific cell of interest. Such modifications include modification of the sugar residues, modification of the phosphodiester linkage and complete modification of the sugar phosphate backbone. Backbone modifications involve changes to the inter-nucleotide phosphate residue, and can include the replacement of one of the nonbridged oxygen atoms by a CH_3 group or an OR group (see Miller, P., Oligodeoxynucleotides: Antisense Inhibitors of Gene Expression, pp. 85-92, CRC Press, 1989), an NR_2 group (Froehler et al, *Nucleic Acids Res.* 16:4831-4839 (1988)), or a sulfur molecule

(Stein & Cohen, *Cancer Res.* 48:2659-2668 (1988)). Modifications to the nucleoside or to the sugar moiety are discussed in Baker & Monia, *Biochim Biophys Acta* 1489:3-18 (1999) and in Uhlmann & Peyman, *Chem. Rev.* 90:544-579 (1990)).

8. Selection of a useful oligo thus may require experimentation, but the experimentation is routine. Activity of a given oligo can be determined readily through Western blot analysis and/or an XTT cytotoxicity assay. Once an oligo has been shown to have specificity for the target mRNA, its stability or activity can be enhanced through modifications well-known to persons of skill in the art.

9. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

Esther Chang, Ph.D.

6/17/03
Date

Esther H. Chang, Ph.D.
Professor, Department of Oncology and Otolaryngology
Georgetown University Medical Center

In addition to her faculty position at Georgetown University, Dr. Chang is a Consultant Professor in the Department of Surgery at Stanford University. Before joining Georgetown University, Dr. Chang held positions as a cancer expert for the National Cancer Institute (NCI), as a Professor in the Department of Pathology and Surgery at the Uniformed Services University of Health Sciences, and as a Professor in the Department of Surgery at Stanford University. She serves on the Board of Scientific Advisors for NCI and US Military Cancer Institute.

Research: Dr. Chang's efforts focus primarily on the molecular mechanisms of carcinogenesis. Delineation of the roles of various genetic factors in the multistep process of tumor formation is the key to improved diagnosis and effective therapy of cancer. Dr. Chang has been a contributor to the understanding of the effects of these genetic influences on many of the events leading to neoplasms. More recently, her research group has been evaluating the combination of systemic, tumor targeted gene therapy and more conventional radiotherapy or chemotherapy for treatment of cancers. She has written over 120 publications and has been appointed to a number of professional advisory boards. Her scientific papers, some of which were widely cited following their respective years of publication, have appeared in prominent journals such as *Nature*, *Science* and *Human Gene Therapy*.

PERSONAL

Name: Esther H. Chang
Place of Birth: Chungking, China
Citizenship: U.S. Citizen
Marital Status: Married with 1 daughter (Harford)
Work Address: Departments of Oncology & Otolaryngology
Georgetown University Medical Center
Lombardi Cancer Center/TRB E420
3970 Reservoir Road NW
Washington, DC 20057-1469
Phone: (202) 687-8418
FAX: (202) 687-8434

Home Address: 7508 Vale Street
Chevy Chase, MD 20815
Phone: (301) 913-5964
FAX: (301) 913-5284
Email Address: change@georgetown.edu

EDUCATION

Fu Jen University, Taiwan	B.A.	1968	Biology
Southern Illinois University	Ph.D.	1974	Microbiology

PROFESSIONAL APPOINTMENTS

Trainee
U.S. Naval Medical Research Unit No. 2
Taiwan
1967 - 1968

Research Assistant
Southern Illinois University
1968 - 1971

Teaching Assistant in Immunology and Virology
Southern Illinois University
1971 - 1972

Research Associate
Southern Illinois University
1972 - 1973

Special Dissertation Fellow
Southern Illinois University
1973 - 1974

Visiting Fellow
National Institutes of Health
1974 - 1977

Visiting Associate
National Institutes of Health
1977 - 1978

Cancer Expert
National Cancer Institute
1978 - 1982

Assistant Professor
Department of Pathology
Uniformed Services University of the Health Sciences
1982 - 1983

Associate Professor and Coordinator for Medical Genetics Curriculum
Department of Pathology
1983 - 1988

Uniformed Services University of the Health Sciences Professor, Department of Pathology Research Professor, Department of Surgery Coordinator for Medical Genetics Curriculum Director, Tumor Biology Program Uniformed Services University of the Health Sciences	1988 - 1994
Professor of Surgery (Research) Division of Otolaryngology/Head & Neck Surgery Department of Surgery Stanford University Medical Center	1994 - 1996
Professor of Surgery (Consultant) Division of Otolaryngology/Head & Neck Surgery Department of Surgery Stanford University Medical Center	1996-Present
Professor of Otolaryngology Department of Otolaryngology/Head & Neck Surgery Georgetown University Medical Center Lombardi Cancer Center	1996-Present
Professor of Oncology and Otolaryngology Departments of Oncology and Otolaryngology Georgetown University Medical Center Lombardi Cancer Center	1999-Present

HONORS AND OTHER SPECIAL RECOGNITION

Honor Society of Phi Kappa Phi	1972
Special Dissertation Fellow Southern Illinois University	1973 - 1974
Author, two papers in 100 most-cited papers in Life Sciences, Current Contents, November 5, 1984	1982 - 1983
Conference Organizer-International Conference on Molecular Biology of Neoplasia Taipai, Taiwan	1984
Ad Hoc Reviewer for NIH Study Section	1985
One of six awardees, Visiting Scholar Exchange Program, National Academy of Sciences, American Council of Learned Societies and Social Science Research Council	1986 - 1987
Member, Merit Review Committee, USUHS	1987 - 1989
Ad hoc Member, Review Panel for Assessment of Department of Energy research projects on chemical toxicology	1989
Member, Faculty Senate Education Committee, USUHS	1990 - 1991
Member, Editorial Board of Antisense Research and Development	1990 - Present
Member, Steering Committee on Prescribing of Drugs by Military Psychologists	1991

Chairman, Subcommittee for Faculty Resources for the Educational Program, Institutional Self-Study at USUHS	1991 - 1993
Member, Scientific Advisory Committee on Design Study for Life Span Experiments in Mice on Carcinogenesis and Biological Effects of Heavy Charged Particles, NASA	1992 - 1994
Chairman, Subcommittee to Examine Faculty, Middle States Association Reaccreditation Self-Study, USUHS	1992 - 1993
Ad hoc Member, Special Review Committee, Epidemiology, NCI	1992
Author, one Nature paper in top ten most cited papers in medicine Science Watch, September, 1992	1992
Member, Board of Scientific Counselors, Division of Cancer Biology, Diagnosis and Centers, National Cancer Institute	1993 - 1995
Member, NASA Life and Microgravity Sciences and Applications Advisory Committee	1994 - Present
Member, Interim ad hoc Board of Scientific Counselors, National Cancer Institute, NIH	1995 - 1996
Chair, Molecular Genetics Study Section, U.S. Army Breast Cancer Research Program	1997
Chair, Experimental Gene Therapy, Program Committee AACR Annual Meeting	1999
Member, Board of Scientific Advisors, National Cancer Institute	1999 - 2004
Member , Editorial Board of Cancer Gene Therapy	1999 - Present
Member, Scientific Program Committee. Chair, Gene Therapy Program NCI-EORTC-AACR Symposium	1999
Distinguished Alumni, Fu Jen University	1999
10th Lecturer, Stewart Lectureship	2000
Member, NASA Focus Group - National Academy of Sciences, Committee on Science, Engineering, and Public Policy	2000
Member, Committee of Scientific Advisors, United States Military Cancer Institute	2001 – Present
Ad hoc member, Experimental Therapeutics I + II, Study Section, NIH	2002
Organizer, Conference on "Tumor Specific Delivery by Non-Viral Systems" Maui, Feb. 2003 Sponsored by NCI	2002-2003
Approximately 10 annual invited lectures at national and international conferences and academic and research institutes	1982 - Present

DISSERTATION TITLE

Comparative Studies of Growth Patterns of Ganjam Virus in CE, BHK and VERO and *Aedes albopictus* Cells

RESEARCH ACTIVITIES

Undergraduate

Insect tissue culture. Studied growth pattern of insect line cells (Bombyx, Aedes and Antheraea) and adapted two lines into hemolymph-free media. Gained some experience in the growth of Japanese Encephalitis Virus in insect cells and newborn mice.

Graduate School

Arboviruses (Togaviruses). Electron microscopy. Compared the growth of VSV in insect cells and chicken embryo fibroblasts. Determined the viral RNA profiles in each cell line.

Characterized Ganjam Virus, an ungrouped arbovirus.

Postgraduate

RNA tumor viruses - interferon effect. Studied interferon's inhibitory effect on the replication of murine leukemia virus. (In Robert M. Friedman's laboratory, National Institutue of Arthritis, Metabolic and Digestive Diseases, NIH).

Molecular genetics. Cloned and characterized murine leukemia and sarcoma viruses. Investigated the origin and the functional organization of Harvey murine sarcoma virus. Molecularly cloned four DNA fragments containing human homologous sequences of v-*ras* (2 Harvey and 2 Kirsten) and demonstrated their oncogenic potentials. Studied potential human oncogenes. (In Douglas R. Lowy's Laboratory, Dermatology Branch, National Cancer Institute, NIH).

Current

1) Molecular genetic basis of familial cancer syndrome and the involvement of human oncogenes and tumor suppressor genes in carcinogenesis.
2) Modulation of oncogene expression by sequence-specific antisense oligonucleotides.
3) Molecular basis of cellular radioresistance and radioprotection.
4) Tumor Suppressor Gene Therapy for Cancer (Head and Neck, Breast and Prostate)
5) Ligand directed, tumor-targeted liposome-based systemic gene delivery

MEMBERSHIP IN ORGANIZATIONS AND PROFESSIONAL AFFILIATIONS

Honor Society of Phi Kappa Phi	1973-
American Association for the Advancement of Science	1983-
Society of Chinese Bioscientists in America	1988-
The Wound Healing Society	1991-
American Association for Cancer Research	1993-
American Society of Gene Therapy	1997-

PUBLICATIONS - ESTHER H. CHANG

1. R. M. Friedman, **E. H. CHANG**, J.M. Ramseur and M.W. Myers. Interferon-directed inhibition of chronic murine leukemia virus production in cell cultures: Lack of effect of intracellular viral markers. **J. Virol. 16**: 569-574 (1975).

2. R. M. Friedman, J.C. Costa, J.M. Ramseur, M.W. Myers, F.T. Jay and **E. H. CHANG**. Persistence of the viral genome in interferon-treated cells infected with oncogenic or nononcogenic viruses. **The J. Infectious Diseases 133**: A43-A50 (1976).

3. R. M. Friedman, F. T. Jay, **E. H. CHANG**, M. W. Myers, J. M. Ramseur, S. J. Mims, T. J. Triche, and P.K.Y. Wong. Interferon-directed inhibition of chronic murine leukemia virus production in cell cultures. In: Control of Neoplasia by Modulation of the Immune System. (M.A. Chirigos, ed.), Raven Press, New York (1977), pp. 347-359.

4. R. M. Friedman, E. F. Grollman, **E. H. CHANG**, L. D. Kohn, G. Lee and F. T. Jay. Interferon and glycoprotein hormones. In: Texas Reports on Biology and Medicine (1977), pp. 326-329.

5. R. M. Friedman and **E. H. CHANG**. Interferon action. Possible mechanisms of antiviral activity. In: Interferons and Their Actions (M. Stewart, ed.) CRC Handbook Series (1977), pp. 145-152.

6. **E. H. CHANG,** S. J. Mims, T. J. Triche, and R. M. Friedman. Interferon inhibits mouse leukemia virus release: An electron microscope study. **J. Gen. Viron. 34**: 363-367 (1977).

7. P. K. Y. Wong, P. H. Yuen, R. Macleod, **E. H. CHANG,** M. W. Myers, and R. M. Friedman. The effect of interferon on *de novo* infection of Moloney murine leukemia virus. **Cell 10**: 245-252 (1977).

8. **E. H. CHANG,** M. W. Myers, P. K. Y. Wong, and R. M. Friedman. The inhibitory effect of interferon on a temperature-sensitive mutant of Moloney murine leukemia virus. **Virology 77**: 625-636 (1977).

9. E. **H. CHANG,** and R. M. Friedman. A large glycoprotein of Moloney leukemia vrius derived from interferon-treated cells. **Biochem. Biophys. Res. Commun. 77**: 392-398 (1977).

10. **E. H. CHANG,** F. T. Jay and R. M. Friedman. Physical and morphological alteration in the membrane of AKR cells following interferon treatment and their correlation with the establishment of the antiviral state. **Proc. Natl. Acad. Sci. 75**: 1859-1863 (1978).

11. **E. H. CHANG**, E. F. Grollman, F.T. Jay, G. Lee, L. D. Kohn and R.M. Friedman. Membrane alterations following interferon treatment. In: Human interferon. W. Alton Jones Cell Science Center, Lake Placid, New York (1978), pp. 85-99.

12. A. K. Bandyopadhyay, **E. H. CHANG,** C. C. Levy and R. M. Friedman. Structura abnormalities in murine leukemia viruses produced by interferon-treated cells. **Biochem. Biophys. Res. Commun. 87**: 983-988 (1979).

13. G. L. Hager, **E. H. CHANG,** H. W. Chan, C. F. Garon, M. A. Israel, M. A. Martin, E. M. Scolnick and D. R. Lowy. Molecular cloning of the Harvey sarcoma virus closed circular DNA intermediates: Initial structural and biological characterization. **J. Virol. 31**: 795-809 (1979).

14. H. W. Chan, C. F. Garon, **E. H. CHANG**, D. R. Lowy, G. L. Hager, E. M. Scolnick, R. Repaske and M. A. Martin. Molecular cloning of the Harvey sarcoma virus circular DNA intermediates: II. Further structural analyses. **J. Virol. 33**: 845-855. (1980).

15. A. I. Oliff, G. L. Hager, **E. H. CHANG,** E. M. Scolnick, H. W. Chan and D. R. Lowy. Transfection of molecularly cloned Friend murine leukemia virus DNA yields a highly leukemogenic helper independent type C virus. **J. Virol. 33**: 475-486 (1980).

16. S. L. Berger, M. J. Hitchcock, K. C. Zoon, C. S. Birkenmeier, R. M. Friedman and **E. H. CHANG**. Characterization of interferon messenger RNA synthesis in namalva cells. **J. Biol. Chem. 255:** 2955-2961 (1980).

17. E. **H. CHANG**, J. Maryak, D. M. Wei, T. Y. Shih, R. Shober, H. L. Cheung, R. W. Ellis, G. L. Hager, E. M. Scolnick and D. R. Lowy. Functional organization of the Harvey murine sarcoma virus genome. **J. Virol. 35**: 76-92 (1980).

18. R. W. Ellis, D. DeFeo, J. M. Maryak, H. A. Young, T. Y. Shih, **E. H. CHANG,** D. R. Lowy and E. M. Scolnick. A dual evolutionary origin for the rat genetic sequences of Harvey murine sarcoma virus. **J. Virol. 36**: 408-420 (1980).

19. **E. H. CHANG** and D. R. Lowy. Transformation by molecularly cloned Harvey murine sarcoma virus DNA. **J. Supramol. Struc. 9 (Supp. 4)**: 237 (1980).

20. E. M. Scolnick, T. Y. Shih, J. Maryak, R. Ellis, **E. H. CHANG** and D. Lowy. Guanine neucleotide binding activity of *src* gene product of rat-derived murine sarcoma viruses. **Ann. N.Y. Acad. Sci. 354**: 398-409 (1980).

21. **E. H. CHANG**, R. W. Ellis, E. M. Scolnick and D. R. Lowy. Transformation by cloned Harvey murine sarcoma virus DNA: Efficiency increased by long terminal repeat DNA. **Science 210**: 1249-1251 (1980).

22. D. DeFeo, M. A. Gonda, H. A. Young, **E. H. CHANG**, D. R. Lowy, E. M. Scolnick and R. W. Ellis. Analysis of two divergent rat genomic clones homologous to the transforming gene of Harvey murine sarcoma virus. **Proc. Natl. Acad. Sci. 78**. 3328-3332 (1981).

23. D.R. Lowy, R.W. Ellis, D. DeFeo, **E. H. CHANG**, M.A. Gonda, H.A. Young, N. Tsuchida, T.Y. Shih and E.M. Scolnick. The cellular p21 sarc genes represent a family of divergent normal genes which have the capacity to transform mouse cells. In: RNA Tumor Viruses, New York, Cold Spring Harbor (1981), p. 294.

24. D.R. Lowy, R.W. Ellis, D. DeFeo, **E. H. CHANG**, M.A. Gonda, A. Young, T.Y. Shih and E.M. Scolnick. The family of cellular P21 sarc genes. In: Intl. Union of Microbiol. Soc., Virology Division (1981), p. 462.

25. **E. H. CHANG**, D.R. Lowy, M. Gonda, D. DeFeo, E.M. Scolnick and R.W. Ellis. The p21 gene family: Human and rodent DNA sequences homologous to the transforming genes of Harvey and Kirsten murine sarcoma viruses. In: Advances in Comparative Leukemia Research (1981), pp. 379-380.

26. D. R. Lowy. **E. H. CHANG**, R. W. Ellis, D. Defeo and E. M. Scolnick. Elevated levels of an evolutionarily conserved normal rat protein can induce cellular transformation. **Clin. Res. 29(2):** 428 (1981).

27. S. K. Chattapadhyay, **E. H. CHANG**, M. R. Lander, R. W. Ellis, E. M. Scolnick and D. R. Lowy. Selective amplification of *onc* genes in mammalian species. **Nature 296**: 361-363 (1982).

28. D. R. Lowy, **E. H. CHANG**, R. M. Ellis, M. A. Gonda, T. Shih, D. DeFeo and E. M. Scolnick. Harvey and Kirsten sarcoma viruses and the P-21 gene family. **J. Cell Biochem. Suppl. 6**: 194 (1982).

29. **E. H. CHANG**, M. A. Gonda, R. W. Ellis, E. M. Scolnick and D. R. Lowy. The human genome contains four genes homolgous to the transforming genes of Harvey and Kirsten murine sarcoma viruses. **Proc. Natl. Acad. Sci. 79**: 4848-4852 (182).

30. **E. H. CHANG**, M. A. Furth, E. M. Scolnick and D. R. Lowy. Tumorigenic transformation of mammalian cells induced by a normal human gene homologous to the oncogene of Harvey murine sarcoma virus. **Nature 297**: 497-483 (1982).

31. D. R. Lowy, M. A. Gonda, M. E. Furth, R. W. Ellis, E. M. Scolnick, and **E. H. CHANG.** Tumorigenic transformation of mammalian cells induced by elevated levels of a normal human *onc* protein. **Clin. Res. 30(2)**: 421 (1982).

32. C. J. Tabin, S. M. Bradley, C. L. Borgmann, R. A. Weinberg, A. G. Papageorge, E. M. Scolnick, R. Dhar, R. Lowy and **E. H. CHANG**. Mechanism of activation of a human oncogene. **Nature 300**: 143-149 (1982).

33. B. D. Crawford, **E. H. CHANG**, J. L. Goodwin, C. E. Hildebrand, P. M. Kraemer, J. L. Longmire and R. D. Palmiter. **J. Cell Biochem. Suppl.** 7: 135 (1983).

34. **E. H. CHANG**, M.A. Gonda, M.E. Furth, J.L. Goodwin, S.E. Yu, R.W. Ellis, E.M. Scolnick and D.R. Lowy. Characterization of four members of the p21 gene family isolated from normal human genomic DNA and demonstration of their oncogenic potential. In: Gene Transfer and Cancer, Raven Press, New York (1983), pp. 189-197.

35. **E. H. CHANG**, M.A. Gonda, E.M. Scolnick and D.R. Lowy. Characterization of 4 divergent human genomic clones homologenes to the transforming p21 genes of Harvey and KiMuSV. In: Gene to Protein--Translation into Biotechnology, American Press (1983), p. 512.

36. D.R. Lowy, M.A. Gonda, M.A. Furth, R.W. Ellis, E.M. Scolnick and **E. H. CHANG**. The human genes homologous to p21 *ras* viral oncogenes. In: Tumor Viruses and Differentiation, Alan R. Liss, Inc., (1983), pp. 435-444.

37. D. Samid, **E. H. CHANG** and R.M. Friedman. Revertants from interferon-treated mouse cells transformed by a human oncogene. In: The Biology of the Interferon System, Elsevier Science Publishers, (1983), pp. 359-360.

38. M. S. McCoy, J. J. Toole, J. M. Cunningham, **E. H. CHANG**, D. R. Lowy and R. A. Weinberg. Characterization of a human colon/lung carcinoma oncogene. **Nature 302**: 79-81 (1983).

39. S. J. O'Brien, W. G. Nash, J. L. Goodwin, D. R. Lowy and **E. H. CHANG**. Dispersion of the *ras* family of transforming genes to four different chromosomes in man. **Nature 302**: 839-842 (1983).

40. M. R. Pincus, J. van Reswoude, J. B. Harford, **E. H. CHANG** and R. D. Klausner. Prediction of the three-dimensional structure of the transforming region of the EJ/T24 human bladder oncogene product and its normal cellular homologue. **Proc. Natl. Acad. Sci. 80**: 5253-5257 (1983).

41. S. J. O'Brien, W. G. Nash, R. Bauer, **E. H. CHANG** and L. J. Seigel. Trends in chromosomal and oncogene evolution in vertebrates. "Uses and Standardization in Vertebrae Culture Cells" (M. K. Paterson, ed.), *IN VITRO* **Monograph No. 5**: Gaithersburg Tissue Culture Association (1984), pp. 204-214.

42. D. Samid, **E. H. CHANG** and R. M. Friedman. Biochemical correlates of reversion in interferon-treated mouse cells transformed by a human oncogene. **Biochem. Biophys. Res. Commun. 119:** 21-28 (1984).

43. D. Samid, **E. H. CHANG** and R. M. Friedman. Inhibition by interferon of transformation induced by a human *ras* oncogene. **Biochem. Biophys. Res. Commun. 126(1):** 509-516 (1985).

44. D. Samid, Z. Schaff, **E. H. CHANG** and R.M. Friedman. Reduction in *ras* expression accompanies phenotypic reversion of interferon-treated, c-Ha-*ras* oncogene transformed mouse cells. In: The Biology of the Interferon System (H. Kirchner and H. Shellekens, eds.), Elsevier, Amsterdam (1985), pp. 189-198.

45. D. Samid, Z. Schaff, **E. H. CHANG** and R. M. Friedman. Interferon-induced modulation of human *ras* oncogene expression. Endocoids. In: Progress in Clinical and Biological Research, Vol. 192 (H. Lal, F. La Bella and J. Lane, eds.), Alan R. Liss, New York (1985), pp. 265-268.

46. D. Samid, **E. H. CHANG** and R.M. Friedman. Specific inhibition by interferon of oncogene-induced transformation. In: Serono Symposia Publications, Vol. 24 (F. Dianzani and G.B. Rossi, eds.), Raven Press, New York, (1985), pp. 425-422.

47. D. Samid, D.M. Flessate, J.J. Greene, **E. H. CHANG** and R.M. Friedman. Mechanisms of Antioncogenic activity of interferon in the 2-5A System: Molecular and clinical aspects of the interferon-regulated pathway. In: Prigin. Clinical and Biological Research, Vol. 202, (B.R.G. Williams and R.H. Silverman, eds.), Alan R. Liss, New York (1985), pp. 203-210.

48. D. Samid, **E. H. CHANG** and R.M. Friedman. Regulation of *ras*-expression by interferon. In: Proc. Asian Congress Pharmacol., (1985), pp. 343-364.

49. **E. H. CHANG**, J.K. Lin, and P. C. Huang, eds. Molecular Biology of Neoplasia. Academia Sinica, 1985

50. **E. H. CHANG**. Viral and cellular oncogenes. In: Molecular Biology of Neoplasia. (E.H. Chang, J.K. Lin and P.C. Huang, eds.) Academia Sinica - Taipei, Taiwan (1985), pp. 191-203.

51. D. Samid, **E. H. CHANG**, and R. M. Friedman. Biological and morphological characteristics of phenotypic revertants appearing in interferon-treated mouse cells transformed by a human oncogene. **J. Exp. Path. 2(3)**: 211-222 (1985).

52. **E. H. CHANG**, P. L. Morgan, E. Lee-Lawlor, K. Pirollo, E. A. White, P. N. Tsichlis and D. H. Patrick. Pathogenicity of retroviruses containing either normal human c-Ha-*ras* 1 or bladder carcinoma EJ/T24 *ras* gene. **J. Exp. Path 2:** 177-190 (1985).

53. R. L. Stallings, R. Black, B. D. Crawford and **E. H. CHANG**. Assignment of *ras* protooncogenes in Chinese hamster: Implications for linkage conservation. **Cytogenet. Cell Genet. 43:** 2-5 (1986).

54. **E. H. CHANG**, R. Black, T. Masnyk and J.B. Harford. Effect of interferon on growth of A431 cells and expression of EGF receptors. In: Advances in Gene Technology: Molecular Biology of the Endocrine System. (D. Puett, *et al*, eds.), Proc. 18th Annual Miami Winter Symposium, 1986, pp. 370-371.

55. **E. H. CHANG**, R. Black, Z.Q. Zou, T. Masnyk, J. Ridge, P. Noguchi and J.B. Harford. Interferon modulates growth of A431 cells and expression of EGF receptors. In: Interferons as Cell Growth Inhibition and Antitumor Factors. (R.M. Friedman, T. Merigan and T. Sreevalsan, eds.), Alan R. Liss, New York (1986), pp. 335-350.

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THESIS AND DISSERTATION

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PATENT - APPLICATION FILED

1. c-Raf Transgenic Non-Human Mammals.
2. An Automated Method for the Detection of p53 Mutations.
3. Treatment of Tumors by a Combination of Radiation Therapy and Transduction with Polynucleotide Encoding Wild Type p53.
4. Method of Reversal of Resistance to Radiation Therapy and to Chemotherapy in Cancer Cells Using Sequence-Specific Anti-HER-2 Oligonucleotides.
5. Modified Antisense Nucleotides Complementary to a Section of the Human Ha-*ras* Gene.
6. Targeted Liposome Gene Delivery.
7. Compositions and Methods for Reducing Radiation and Drug Resistance in Cells.
8. Systemic Viral/Ligand Gene Delivery System and Gene Therapy.
9. Ligand-PEG "Post-coated" Cationic Liposomes for Targeted Gene Delivery.
10. Antibody Fragment-Targeted Immunoliposomes for Systemic Gene Delivery.
11. A Simplified and Improved Method for Complexing an Antibody Fragment-Targeted Immunoliposome for Systemic Gene Delivery.